ORIGINAL ARTICLE

Serum Uric Acid as A Biomarker in Bipolar Disorder Type I, Current Episode Manic-Hospital Based Cross-Sectional Study

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ABSTRACT

Objective: To compare serum uric acid in bipolar disorder (BD) type I patients, current episode manic with healthy matched controls.

Study Design: Our study had a cross-sectional, case-control design.

Place and Duration of Study: This research was done at Rawal General & Dental Hospital which is the tertiary care teaching hospital of Rawal Medical & Dental College, Islamabad. The period of study was from 1/10/2023 to 31/03/2024 for a period of 6 months.

Materials and Methods: Thirty patients with BD suffering from manic episode according to DSM-5 criteria, along with 30 matched healthy controls were enlisted in the study. Young Mania Rating Scale (YMRS) was administered to the patients to determine the severity of mania and serum uric acid was determined for both cases and healthy controls (HC). The data was analyzed with Statistical Package for Social Sciences version 22 (SPSS).

Results: Compared to HC (4.4 ± 0.9mg/dl) bipolar patients had elevated plasma uric acid levels (6.06 ± 1.48 ml/dl) [$p = 0.018$]. Age and gender were the two factors that could introduce bias, but after controlling for these, the results were still significant. In the cases YMRS was used to measure the severity of the manic episode, and serum uric acid levels did not have a correlation with this variable ($P > 0.683$).

Conclusion: The level of serum uric acid was significantly higher in cases versus controls in the local population. These results were in line with international studies and pointed to aberrant purine nucleotide turnover in BD.

Key Words: *Bipolar Disorder, Inflammation, Mania, Purine Metabolism, Uric Acid.*

Introduction

Bipolar disorder (BD) is a severe psychiatric condition whose pathophysiological underpinnings are largely unknown.[1] Different pathways involved in the development of BD include abnormalities in neurotransmission, neuroinflammation and neurodegenerative mechanisms.[2] One line of research incriminates purinergic system dysfunction in the neurobiology of BD.[3,4] Adenosine triphosphate (ATP) stored in the cells, serves as the essential energy substrate for vital cellular functions. Diverse mechanisms are involved through which ATP reaches the extracellular space; in turn, neurons express purinergic receptors and binding of the extracellular ATP stimulates many intracellular signaling cascades.[5] The majority of purinergic receptors are located in the hippocampus where they may be involved in such vital processes as the formation of new neurons.[6] Ectoenzymes expressed on the cell surface hydrolyze ATP into adenosine and precisely control extracellular purine concentration.[7] Adenosine wields several functions in the brain via its own receptors, and crucially these include neuroprotection. ATP and adenosine have regulatory immune functions; the former triggers proinflammatory pathways, whereas adenosine acts to dampen inflammation.[8] Increased levels of ATP in the extracellular compartment promote excitotoxicity and neurodegeneration, processes incriminated in the pathophysiology of major neuropsychiatric disorders like BD.[9]

Adenosine is broken down into uric acid (UA), the main nitrogenous end product of purine metabolism and in BD, may serve as a possible indicator of treatment response. Further, during manic episode high serum levels of uric acid may have value as a state marker.[10] It is surmised that raised serum uric

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acid levels specify enhanced purine turnover and diminished adenosine signaling in the CNS. Recent evidence shows that the purinergic system is incriminated in several key brain functions such as mood, sleep, cognitive function, motor activity and behavior.[11] Lesch Nyhan syndrome, regarded as a dysfunction in the purinergic system is exemplified by the production of large amounts of uric acid and raised uric acid levels are linked to impulsivity and irritability in these individuals.[12]

A systematic review and meta-analysis of randomized controlled studies indicated that allopurinol, a modulator of purine metabolism and a xanthine oxidase inhibitor, was helpful in the treatment of acute mania when used in conjunction with lithium.[13] It showed that decrease in YMRS scores from the start to the endpoint was related to a decline in plasma uric acid levels; also, patients who remitted were significantly more likely to have a lower serum uric acid levels as compared to non-remitters.[13] Ostensibly, this implied that uric acid levels were the representative marker of clinical efficacy besides acting as a biomarker during the manic phase of BD.[14] While there is an increasing body of research investigating serum uric acid levels in BD internationally, we could not find any study on this topic in the local context signifying an important gap in the knowledge from our perspective. The objective of the present study was to examine serum uric acid levels in BD subjects in the manic phase and compare those to healthy controls.

Materials and Methods

This was a cross-sectional case-control study and not an observational study. The control group was selected from patients' attendants and hospital visitors provided they gave informed consent. The criteria for selection were that the control subjects must not be suffering from any medical illness and had no past psychiatric history. Thirty bipolar disorder patients in the manic phase according to DSM-V criteria presenting to the Psychiatry Department of Rawal General Hospital were included and these were compared to 30 healthy controls. The sample size was calculated with the help of the formula given below:

$$\text{Unlimited population: } n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

$$\text{Finite population: } n' = \frac{n}{1+\frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2 N}}$$

where
z is the z score
ε is the margin of error
N is the population size
p̂ is the population proportion

The population size was 60, the population proportion was 50%; confidence interval was 95% and margin error was 5%. Also guidance was sought from a recently published article in the PubMed database.[15] The sampling technique was convenience, non-purposive and consecutive. The duration of study was from 1/10/2023 to 31/03/2024 for a period of 6 months. Permission to conduct the study was given vide ethical review board approval letter reference number RIHS/DME/07/2023 of Rawal Medical & Dental College, Islamabad.

The study was done in strict compliance with the code of conduct enshrined in the Helsinki Declaration of 2013. It was made certain that no harm would come to any of the participants and confidentiality was maintained at all times. Furthermore, informed consent from all the study subjects was ensured.

The subjects included were aged between 18 and 60 years and suffering from bipolar disorder type I, current episode manic. Excluded from the study were patients who were medically unstable, or suffering from chronic inflammatory conditions. Similarly, patients with gout or any other disease causing hyperuricemia were also left out. Lastly, subjects with a history of heavy smoking or substance abuse were barred from the study.

Psychometric assessment of the bipolar patients was done by administering the Young Mania Rating Scale (YMRS). This is the preferred instrument in research and has good validity and reliability. It comprises of 11 items which are centered on patients' own report of their clinical state during the last 48 hours. The test items are based on the main symptoms of mania, administered by the clinician and rated from 0 to 60 with a cut-off score of 20 in manic subjects. Strong points of the YMRS are its conciseness, simplicity and general acceptability. YMRS was done only once since this was a cross-sectional study to examine

whether severity of mania correlated with serum uric acid levels. In addition, both cases and controls were administered a demographic proforma.

Laboratory assessment was done by taking venous blood samples from both patients and controls using vacutainer tubes. These were centrifuged at 3000×g for 15 min and stored at −80 °C until chemical analysis to determine the value of serum uric acid.

Statistical analysis was done by using SPSS version 22. With respect to demographic variables, Chi-square test was used for categorical variables and Mann-Whitney U test for continuous variables. In order to compare uric acid levels between patients and controls analysis of variance was used. We followed the null hypothesis which stated that there was no difference in the mean serum uric acid levels of cases and controls. The F test in one-way ANOVA compared the primary outcome i.e. variability within groups to variability between groups. For correlation analysis Pearson's correlation coefficient was used. All of the tests were two ended, and a p value of <.05 was considered as significant.

Results

Table I showed the relationship between patients and controls with respect to demographic variables. It could be seen that the two groups were comparable as regards age, gender, marital status, etc. and no statistically significant difference was found between them. Bipolar subjects suffering from manic episode demonstrated greater plasma uric acid levels (6.06 ± 1.48 ml/dl) as compared to healthy controls (4.4 ± 0.9mg/dL) (p = 0.018) (Table II). Analysis of variance was utilized in the SPSS, also referred to as one way ANOVA and plasma uric acid was controlled for age and gender. However, the results remained significant such that these factors did not introduce bias in the study. No correlation was found between serum uric acid levels and the severity of manic episode as assessed by using the YMRS (P >0.683), (Table III).

Table I:Comparison of Sociodemographic Variables of Healthy Controls and Bipolar Disorder Patients

Variables	BD group N=30	HC N=30	*P*
Age	37 (CI: 30-45)	34 (CI: 29-44)	0.135[a]
Age range 18-25	10 (CI: 20-30)	8 (CI: 18-32)	0.231[a]
Age range 26-45	12 (CI: 22-48)	14 (CI: 24-50)	0.174[a]
Age range 46-60	18 (CI: 38-68)	8 (CI: 41-66)	0.428[a]
Male	21 (70%)	15 (50%)	0.537[b]
Female	9 (30%)	15 (50%)	0.512[b]
Single	10 (33%)	12 (40%)	0.339[b]
Married	20 (66%)	18 (60%)	0.278[b]
Years married < 10	10 (50%)	8 (44%)	0.174[a]
Years married > 10	10 (50%)	10 (56%)	0.295[a]
Married with children	18 (90%)	16 (88%)	0.362[b]
Education (years)	12 (CI: 8-16)	10 (CI: 7-14)	0.174[a]
Not working	6 (20%)	8 (26%)	0.475[b]
Working	24 (80%)	22 (74%)	0.483[b]

BD – bipolar disorder; CI – confidence interval; HC – healthy control; [a]Mann-Whitney U test; [b]Chi-square test

Table II: Comparison of Serum Uric Acid Levels of BD Subjects and Healthy Controls

	BD Manic Episode	Healthy Control	Variability within Groups	Variability between Groups	*P* value
Uric acid level (mg/dl)	6.06 ± 1.48	4.4 ± 0.9	6.122 (95% CI 5.837 – 6.847)	6.361 (95% CI 5.915 – 6.914)	0.018*

BD Bipolar Disorder; * One Way ANOVA (Analysis of Variance); CI Confidence Interval

Table III: Relationship Between YMRS Scores and Serum Uric Acid

Serum uric acid (mean)	YMRS scores (mean)	Pearson's correlation coefficient
6.06 ± 1.48	26 ± 8	>0.683

YMRS Young Mania Rating Scale

Discussion

Our study showed that serum uric acid levels were significantly higher in bipolar disorder patients versus controls. This finding points toward an abnormality in purinergic system in bipolar disorder, at least in the manic phase. A well-cited European study compared bipolar disorder patients with subjects who were suffering from other main psychiatric illnesses like major depressive disorder, obsessive compulsive disorder and schizophrenia. It reported that uric acid levels were raised in BD subjects in comparison with patients in other diagnostic groups and that these remained elevated in all phases of BD, even in euthymic subjects. The study concluded that higher serum uric acid levels might be trait makers in bipolar illness with further rises in the manic phase, such that elevated uric acid

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levels may be a state marker of the manic state.[16] Another study examined bipolar subjects in mania, depression and remission and compared them to healthy controls. In comparison to healthy controls, uric acid levels were found higher in all three phases of BD, i.e. mania, depression and euthymia. A modest relationship was shown in the manic episode between 1st and 2nd week YMRS scores and uric acid levels, and a robust correlation was discovered in the depressive episode between 1st and 2nd week Hamilton Rating Scale for depression scores and uric acid levels. In the manic episode a reduction in serum uric acid level was found to be related to decrease in YMRS scores, whereas a similar relationship was not shown in the depressive episode. These results indicate the possible occurrence of purinergic dysfunction in bipolar subjects, which appear to be associated with all phase of the disorder.[17]

A study investigated serum uric acid levels in drug free, index episode mania cases and compared them to healthy subjects who acted as controls. It was discovered that patients in acute mania had significantly greater levels of serum uric acid compared to HC. No association was seen between the levels of serum uric acid and the severity of mania. These findings suggest that serum uric acid levels represent state marker of bipolar disorder in the manic phase. Moreover, the presence of disturbance in purine nucleotide metabolism in these patients has implications for disordered adenosinergic neurotransmission.[18] This study is important because it demonstrates purinergic dysfunction in first-episode, drug-naïve manic patients. Elevated uric acid in these patients suggests that abnormality in purine nucleotide metabolism is inherent to BD and not a result of chronicity or secondary to the administration of psychotropic medications. Our study seems to replicate some of these findings, particularly the non-significant relationship between YMRS scores and serum uric acid levels. It can be concluded that serum uric acid levels while elevated in the manic phase of BD, do not have a significant relationship with the severity of mania.

Raised serum uric acid levels points towards enhanced purinergic transformation and diminished adenosinergic signaling in the CNS. The latter serves to decrease the excitability of neurons by reducing the release of neurotransmitters.[19] Uric acid specifically acts on adenosine A1 receptors in the limbic areas of the brain and increased level of this final metabolite of purine turnover is supposedly liable for the kindling, excitoxic action. Extending from animal models, this is considered to be the primary association between adenosinergic activity and manic symptoms.[20] Hence, lithium which is the gold standard mood stabilizer purportedly decreases uric acid levels and a comparable mechanism has been described for carbamazepine, while conversely sodium valproate has been found to raise serum uric acid levels.[21]

An interesting study tested the relationship between bipolar disorder and serum uric acid levels, seeking to clarify whether this association was caused by metabolic syndrome and related indices. One hundred and seventy six patients suffering from a variety of psychiatric disorders and 89 healthy controls were included in the study.[22] Among the patients, bipolar disorder was the single diagnostic subclass significantly linked to higher uric acid levels. Furthermore, variables including male sex, metabolic syndrome, increased abdominal circumference and raised serum triglycerides levels had a significant effect on uric acid. Statistical analysis disclosed that the probable effect between bipolar disorder and uric acid levels was only partly the result of metabolic abnormalities. These finding suggest a direct linkage between bipolar disorder and uric acid levels, which is not the result of any associated metabolic abnormalities.[22]

Finally, an innovation in medicine is the application of uric acid linked ratios in different diseases such as diabetes mellitus. The use of these in bipolar disorder was recently reported in a study from the Peoples Republic of China. Noteworthy ratios included uric acid-to-albumin ratio (UAR), uric acid-to-creatinine ratio (UCR), uric acid-to-high-density lipoprotein ratio (UHR), and uric acid-to-lymphocyte ratio (ULR). It was shown that in comparison to healthy controls and subjects with bipolar depression, manic patients had higher ULR, UHR, UCR and UAR. Moreover, in cases with psychotic mania these ratios were even higher when compared to patients with non-psychotic mania. The study concluded that the inflammatory response was more intense in bipolar mania than depression and that

UAR was a risk factor for mania.[23]

We conducted a search of the literature to investigate whether any studies were done locally on the topic of serum uric acid levels and BD. To our dismay we could not find any study on this subject specifically. As such ours is a pioneering study in the local population and because of the importance of uric acid as a marker in bipolar disorder we hope that other researchers from our country will investigate this area further.

Limitations

1) The present study is cross-sectional in nature and in order to validate the results a study with longitudinal, prospective design is needed.
2) The sample size is small and a study with larger sample is needed to corroborate the findings of this study.
3) A multi-centered study, preferably with a multi-national design is required to further examine the utility of serum uric and uric acid related ratios as biomarkers in bipolar disorder.
4) We employed convenience sampling which could have introduced selection bias.
5) We did not control for metabolic syndrome which was a possible source of bias in the study.

Conclusion

Our study shows that serum uric acid may serve as a biomarker in the manic phase of bipolar disorder. This is an inexpensive and readily available test which may be a state marker of mania. Furthermore uric acid related ratios enhance the value of this parameter in bipolar illness, as these are indicative of an inflammatory state in the manic phase. It is hoped that further research will clarify the status of uric acid as a biomarker in BD.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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